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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,823	02/12/2002	Waldemar Debinski	6460-41	8785

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,823	DEBINSKI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *2-8 and 19-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-43 are pending.

2. Claims 2-8 and 19-43 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 4/4/05, the following rejections remain.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 9-11 and 13-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,235,713 B1 (filed Aug 1997; PTO 892) in view of US Pat No. 5,874,290 (Feb 1999; PTO 892).

The '713 patent teaches a method of detecting VEGF-D in a biological sample comprising the steps of contacting the sample with a probe such as monoclonal and polyclonal antibody that bind specifically to VEGF-D and detecting the binding by means of a detectable label (see col. 6, lines 66-67 bridging col. 7, lines 1-7, col. 5, lines 51-67, in particular). The reference VEGF-D is a native VEGF-D protein (see col. 19, lines 34-42, VEGFD fullFLAG, in particular) and proteolytic cleaves to produce product comprises a VEGF-D homology domain

(see col. 19, line 25, VEGFDΔNΔC, in particular). The '713 paten teaches VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the method for detecting a cancer in a brain tissue sample instead of any biological sample.

The invention in claim 9 differs from the teachings of the reference only in that the method for detecting a cancer in a human brain tissue sample instead of any biological sample.

The '290 patent teaches various VEGFs that have been shown to overexpressed in different types of brain tumors (see co. 3, lines 5-14, and references therein, in particular). The '290 patent further teaches the use of fetal brain tissue and cell lines derived from human such as human glioblastoma multiforme tumor tissue for diagnosis of brain tumor using specific VEGF markers (see col. 43, lines 35-62, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute any biological sample as taught by the '713 patent for the specific human brain tissue derived from human such as human glioblastoma multiforme tumor tissue or biopsy as taught by the '290 patent and '713 patent for a method of detecting VEGF-D in brain tissue. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '290 patent teaches various VEGFs have been shown to overexpressed in different types of brain tumors (see co. 3, lines 5-14, and references therein, in particular). VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk as taught by the '713 patent (see col. 6, lines 16-18, in particular).

Applicants' arguments filed 4/4/05 have been fully considered but are not found persuasive.

Applicants' position is that Applicants invention is directed in part to the detection of cancer in a brain sample by detection of a VEGF-D marker. Applicant's teach the detection of VEGF-D is enhanced in malignant brain tissue and is aberrantly expressed in astrocytomas. Further, applicant's teach that VEGF-D is an X- linked factor and it would not be obvious that VEGF-D is expressed in brain tumors (See for example, page 36 lines 15-33). The Examiner acknowledges that the '713 patent differs from the instant invention in that the '713 patent does

not teach or disclose that VEGF-D is detectable in brain tumors, nor does it suggest or disclose that VEGF-D is a potential tumor marker. The '290 patent does not teach or disclose that VEGF-D is overexpressed in tumors. VEGF was detected in some brain tumors but the '290 patent does not teach or disclose detection and overexpression of VEGF-D as a diagnostic marker of brain tumor. The '713 patent in view of the '290 patent doe not prove any teaching or motivation to one of ordinary skill in the art to combine the teachings of both patents to arrive at the instant invention.

In response to applicant's argument that VEGF-D is an X- linked factor and it would not be obvious that VEGF-D is expressed in brain tumors, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See MPEP 2145.

In response to applicant's argument that there is no suggestion or motivation to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teaching of '713 patent pertaining to VEGF-D is useful as a clinical diagnostic marker in cancer specimens and the teachings of the '290 patent pertaining to various VEGFs have been shown to overexpressed in brain tumor such as human glioblastoma multiforme tumor tissue would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art, that is, detecting VEGF-D in brain tumor. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

7. Claims 12 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,235,713 B1 (of record, filed Aug 1997; PTO 892) in view of US Pat No. 5,874,290 (of record, Feb 1999; PTO 892) as applied to claims 1, 9-11 and 13-17 mentioned above and further in view of Stacker et al (of record, J. Biol. Chem. 274(45): 32127-32136; Nov 1999; PTO 1449) and Achen et al (of record, Eur. J. Biochem. 267: 2505-2515, May 2000; PTO 1449).

The combined teachings of the '713 patent and the '290 patent have been discussed supra.

The invention in claim 12 differs from the combined teachings of the references only in that the method for detecting a cancer in a brain tissue sample wherein the VEGF-D protein is proteolytic cleavage product comprises a VEGF-D homology domain.

The invention in claim 18 differs from the combined teachings of the references only in that the method for detecting a cancer in a brain tissue sample wherein the monoclonal antibody is VD1.

Stacker et al teach VEGF-D is proteolytically processed to generate a bioactive fragment such as VEGF-D homology domain (VHD) (see page 32128, col. 1, first full paragraph, Figure 1, in particular). Stacker et al further teach polyclonal antibody that binds specifically to VHD (see page 32128, Antisera, in particular).

Achen et al teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that bind specifically to the VEGF-D homology domain (VHD) (see page 2507, col. 2, Results, production of anti-VEGF-D mAbs, page 2508, col. 2, last paragraph, in particular). Achen et al teach the reference antibody VD1 could block the mitogenic response of vascular endothelial cells to VEGF-D (see page 2512, col. 1, in particular) and strongly inhibits the binding of VEGFDΔNΔC or the VEGF-D homology domain (VHD) to both VEGFR2 and VEGFR3 (see page 2511, col. 1, last par, in particular). Achen et al teach that these antibodies are useful for analyzing lymphangiogenesis induced by VEGF-D and its contribution to metastatic spread (see page 2513, col. 1, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the VEGF-D specific antibody as taught by the '713 patent for the VD1 monoclonal antibody that binds specifically to the VEGF-D homology domain (VHD) as taught by Achen et al or the polyclonal antibody that binds specifically to the VEGF-D homology domain (VHD) as taught by Stacker et al since the VHD is the active fragment of VEGF-D after proteolytic processing as taught by Stacker et al and Achen et al for a method of

detecting the proteolytic cleavage product of VEGF-D in brain tissue as taught by the '713 patent and the '290 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Stacker et al teach VEGF-D is proteolytically processed to generate a bioactive fragment such as VEGF-D homology domain (VHD) (see page 32128, col. 1, first full paragraph, Figure 1, in particular). Achen et al teach VD1 monoclonal antibody specific to VHD is useful for analyzing lymphangiogenesis induced by VEGF-D and its contribution to metastatic spread (see page 2513, col. 1, last paragraph, in particular). The '290 patent teaches various VEGF have been shown to overexpressed in different types of brain tumors (see co. 3, lines 5-14, and references therein, in particular). The '713 paten teaches VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular).

Applicants' arguments filed 4/4/05 have been fully considered but are not found persuasive.

Applicants' position is that arguments regarding the combined teachings of the '713 and '290 have been discussed. Neither Staker et al, nor Achen et al. standing alone or in combination teach the detection of a VEGF-D homology domain in brain cancer. Since, a normal brain does not have a lymphatic system and GBM does not grow lymphatic vessel, applicants surprising discovery was the ubiquitous detection of the VEGF-D homology domain in the brain.

In response to applicant' argument that Neither Staker et al, nor Achen et al. standing alone or in combination teach the detection of a VEGF-D homology domain in brain cancer, it is noted that the claimed method encompass the use of any anti-VEGF-D antibody. The claims do not require the use of the specific antibody that detects VEGF-D homology domain for the claimed method. Further, the term "comprises" in claim 12 is open-ended. It expands the VEGF-D homology domain to include the whole VEGF-D. The '713 patent teaches antibody to VEGF-D (see col. 6, lines 66-67, bridging col. 7, lines 1-7, lines 51-67, in particular) as well as proteolytic cleaved product such as VEGFDΔNΔC that comprises a VEGF-D homology domain (See col. 19, lines 25, in particular). The teaching of '713 patent pertaining to VEGF-D is useful as a clinical diagnostic marker in cancer specimens and the teachings of the '290 patent pertaining to various VEGFs have been shown to overexpressed in brain tumor such as human

glioblastoma multiforme tumor tissue would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art, that is, detecting VEGF-D in brain tumor. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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